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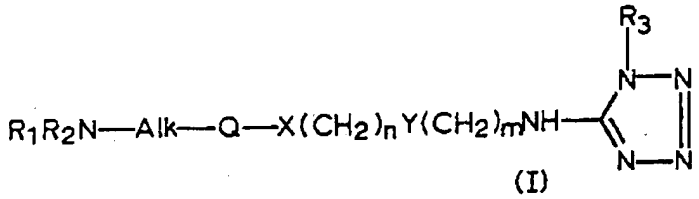
(54) **Tetrazole derivatives**

(57) Compounds of the formula (I)



(I)

and physiologically acceptable salts and hydrates thereof in which

R_1 represents C_{1-14} alkyl, cycloalkyl, aralkyl, trifluoroalkyl, heteroaralkyl, alkenyl, alkynyl, or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or a C_{1-4} alkyl group; or

R_1 and R_2 together with the nitrogen atom to which they are attached form a 5-10 membered ring which is optionally substituted by one or more C_{1-3} alkyl groups or a hydroxy group;

Alk represents a C_{1-8} alkylene chain;

Q represents one of certain divalent radicals derived from benzene, furan or thiophen;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, C_{2-6} alkyl substituted by hydroxy, alkoxy or C_{1-4} alkanoyloxy;

X and Y each represent oxygen, sulphur, methylene or a bond;

n represents zero to 3 and *m* represents 2 to 5 with the provisos that (a) the total number of atoms in the chain $X(CH_2)_nY(CH_2)_m$ is from 3 to 8 and (b) when X and Y represent oxygen or sulphur then n is 2 or 3;

show *pharmacological activity* as selective *histamine H_2-antagonists.*

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The Chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

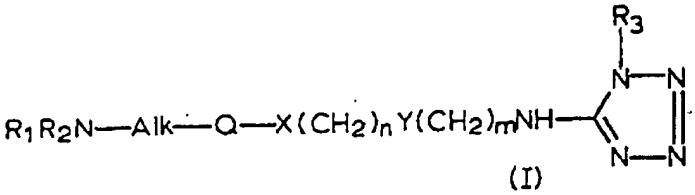
Heterocyclic derivatives

This invention relates to novel heterocyclic derivatives having action on histamine receptors, to processes for the preparation thereof, to pharmaceutical compositions containing them and to their use in therapeutics.

Certain novel heterocyclic derivatives have now been found which have potent activity as H_2-antagonists. These compounds, which are more particularly described below, for example show inhibition of the secretion of gastric acid when this is stimulated via histamine receptors (Ash and Schild, Brit. J. Pharmacol. Chemother, 1966, *27*, 427). Their ability to do so can be demonstrated in the perfused rat stomach using the method described in German Offenlegungsschrift No. 2,734,070, modified by the use of sodium pentobarbitone (50 mg/kg) as anaesthetic instead of urethane, and in conscious dogs equipped with Heidenhain pouches using the method described by Black *et al* Nature 1972 *236*, 385. Furthermore the compounds antagonise the effect of histamine on the contraction frequency of isolated guinea pig right atrium but do not modify histamine-induced contractions of isolated gastro-intenstinal smooth muscle which are mediated via H_1-receptors. Certain compounds according to the invention have the advantage of an extended duration of action.

Compounds with histamine H_2-blocking activity may be used in the treatment of conditions where there is an advantage in lowering gasteric acidity, particularly in gastric and peptic ulceration, as a prophylactic measure in surgical procedures, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. Thus they may be used for example, either alone, or in combination with other active ingredients in the treatment or allergic and inflammatory conditions of the skin.

The present invention provides compounds of the general formula (I)



(I)

and physiologically acceptable salts, hydrates and bioprecursors thereof in which

R_1 represents C_{1-14} alkyl, cycloalkyl, aralkyl, trifluoroalkyl, heteroaralkyl, alkenyl, alkynyl or alkyl substituted by hydroxy, alkoxy, amino, alkyl-amino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or a C_{1-4} alkyl group; or

R_1 and R_2, together with the nitrogen atom to which they are attached, form a 5-10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl groups, e.g. methyl, or a hydroxy group and/or may contain another heteroatom selected from oxygen or sulphur;

Alk represents a straight or branched C_{1-6} alkylene chain.

Q represents a furan or thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 5-positions, the furan or thiophen ring optionally bearing a further substituent R_4 adjacent to the group R_1R_2N-Alk; or Q represents a thiopen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 4-positions, the thiophen ring optionally bearing a further substituent R_4 adjacent to the group R_1R_2NAlk with the proviso that when the group R_1R_2NAlk is in the 4-position then the group R_4 is in the 5-position; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4-positions;

R_4 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, C_{2-6} alkyl substituted by hydroxy, alkoxy or C_{1-4} alkanoyloxy;

X and Y, which may be the same or different, each represent oxygen, sulphur, methylene or a bond;

n represents zero, 1, 2 or 3 and m represents an integer from 2 to 5 with the provisos that (a) the total number of atoms in the chain $X(CH_2)_nY(CH_2)_m$ is an integer from 3 to 8 and (b) when X and Y represent oxygen or sulphur then n is 2 or 3.

The term "alkyl" as a group or part of a group refers to a straight or branched chain group and unless otherwise specified contains from 1 to 6 carbon atoms more preferably 1 to 4 carbon atoms e.g. methyl or ethyl, and the terms "alkenyl" and "alkynyl" mean that the group contains 3 to 6 carbon atoms. The term "cycloalkyl" as a group or part of a group means a group which has 3 to 8 carbon atoms. The term "aryl" as a group or part of a group preferably means phenyl or substituted phenyl, for example phenyl substituted with one or more C_{1-3} alkyl or C_{1-3} alkoxy groups or halogen atoms. The term heteroaryl as a group or part of a group means a 5 or 6 membered monocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, e.g. thienyl, pyrrolyl, pyridyl, furyl or thiazolyl. The heteroaryl ring may be

unsubstituted or substituted by C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or halogen, for example, the heteroaryl ring may be thienyl or furyl substituted by C_{1-3} alkyl, aminoalkyl, alkylaminoalkyl, dialkylamin alkyl or hydroxyalkyl, pyrrolyl substituted by C_{1-3} alkyl, pyridyl substituted by C_{1-3} alkyl, C_{1-3} alkoxy, halogen or hydroxyalkyl or thiazolyl substituted by C_{1-3} alkyl or hydroxyalkyl. The alkyl portion of a heteroaralkyl group is a straight or branched C_{1-4} alkyl chain, and the heteroaryl ring is linked to the alkyl portion through a carbon atom.

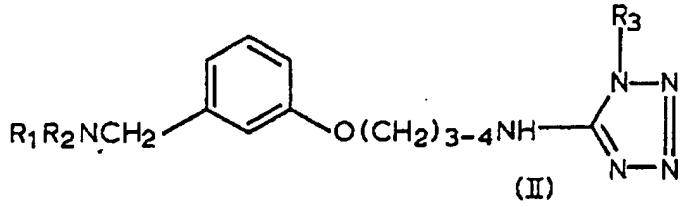
In the compounds according to the invention the chain $X(CH_2)_nY(CH_2)_m$ preferably contains from 4 to 6 atoms. When Q is an optionally substituted furan or thiophene ring the group $X(CH_2)_nY(CH_2)_m$ is preferably $-CH_2O(CH_2)_3-$ or $-(CH_2)_4-$, or more preferably $-CH_2S(CH_2)_2-$. When Q is benzene the group $X(CH_2)_nY(CH_2)_m$ preferably represents $-O(CH_2)_{3-5}$ or $-O(CH_2)_2O(CH_2)_2$. Most preferably Q is a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- positions, and the chain $X(CH_2)_nY(CH_2)_m$ is more particularly $-O(CH_2)_{3-4}$.

Alk preferably represents an alkylene chain containing 1 to 4 carbon atoms, e.g. methylene, ethylene or propylene, more preferably methylene.

R_3 is preferably C_{1-4} alkyl (e.g. methyl, ethyl or propyl), or hydroxy C_{2-4} alkyl (e.g. hydroxyethyl). More preferably R_3 represents C_{1-4} alkyl (e.g. methyl) or hydroxyethyl.

Preferably R_1 represents C_{1-8} alkyl (e.g. methyl, ethyl, propyl, butyl, hexyl or heptyl) or a heteroaryl C_{1-3} alkyl group where the heteroaryl ring contains one heteroatom (e.g. furylmethyl); and R_2 represents hydrogen or methyl; or R_1R_2N represents a saturated 5-7 membered ring optionally containing a double bond or substituted by a hydroxy group (e.g. pyrrolidino, piperidino, tetrahydropyridino or 4-hydroxypiperidino). More preferably R_1R_2N represents di-C_{1-2}-alkylamino (e.g. dimethylamino) or a saturated 5-7 membered ring (e.g. piperidino or pyrrolidino).

A particularly preferred group of compounds are those of formula (II)



(II)

and physiologically acceptable salts, and hydrates thereof, wherein R_1R_2N represents dimethylamino, piperidino or pyrrolidino; and R_3 represents methyl or hydroxyethyl.

Particularly preferred compounds are:

1-methyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1*H*-tetrazol-5-amine;

1-methyl-N-[[3-[3-(dimethylamino)methyl]phenoxy]propyl]-1*H*-tetrazol-5-amine;

1-methyl-N-[3-[3-(pyrrolidinylmethyl)phenoxy]propyl]-1*H*-tetrazol-5-amine; and

5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1*H*-tetrazol-1-(2-ethanol);

and physiologically acceptable salts and hydrates thereof.

The invention includes the compounds of formula (I) in the form of physiologically acceptable salts with inorganic and organic acids. Particularly useful salts include hydrochlorides, hydrobromides and sulphates, methanesulphonates, acetates, maleates, succinates, tartrates, benzoates, citrates and fumarates. The compounds of formula (I) and their salts may also form hydrates, which hydrates are also to be considered as part of the invention. The compounds of formula (I) can exhibit tautomerism and the formula is intended to cover all tautomers. Where optical isomers may exist the formula is intended to cover all diastereoisomers and optical enantiomers. The term bioprecursors as used herein means compounds which have a structure different to that of the compounds of formula (I) but which, upon administration to the animal or human being are converted in the body into a compound of formula (I).

The compounds according to the invention, preferably in the form of a salt, may be formulated for administration in any convenient way and the invention includes within its scope pharmaceutical compositions containing at least one compound according to the invention adapted for use in human or veterinary medicine. Such compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Such compositions may also contain if required other active ingredients, e.g. H_1-antagonists.

Thus the compounds according to the invention may be formulated for oral, buccal, topical, parenteral or rectal administration. Oral administration is preferred.

For oral administration, the pharmaceutical composition may take the form of for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients. For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulation for injection may be presented in unit dosage form in ampoules, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions,

solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

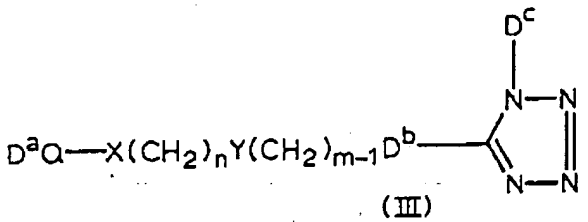
For topical application, the compounds of the invention may be formulated as ointments, creams, gels, lotions, powders or sprays in a conventional manner.

For internal administration a convenient daily dosage regime of the compounds according to the invention is 1 to 4 doses to a total of 5 mg to 1 g per day, preferably 5 to 500 mg per day, dependent upon the condition of the patient.

It will be appreciated in the methods for the preparation of the compounds of formula (I) given below that for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent when R_1 and/or R_2 and/or R_3 are hydrogen and/or when the substituent R_3 is an alkyl group bearing a hydroxy group. Standard protection and deprotection procedures can be employed. For example, an amino group may be protected by formation of a phthalimide group which may subsequently be cleaved by treatment with a hydrazine, e.g. hydrazine hydrate or a primary amine for example methylamine. When R_3 is hydrogen, this may be protected by formation of a N-benzyl or N-alkoxyalkyl (e.g. ethoxymethyl) derivative. The N-benzyl group may subsequently be cleaved by hydrogenolysis in the presence of a catalyst e.g. palladium and an alkoxyalkyl derivative may be cleaved by treatment with dilute acid.

In describing the processes which may be used for preparing the compounds of formula (I) or intermediates useful in the preparation thereof any of the groups R_1, R_2, R_3, Alk, Q, X, Y, n and m are as defined in formula (I) unless otherise stated.

Compounds of formula (I) may be prepared by reducing a compound of formula (III)



(III)

in which D^a may represent R_1R_2NAlk or a group convertible thereto under reducing conditions such as R_1R_2NCO, $R_1^aCONR_2Alk$ (where R_1^aCO represents a group reducible into R_1) or CHO; D^b represents $-CH_2-NH-$, $-CONH-$ or $-CH=N$; and D^c represents R_3 or a group convertible thereto under reducing conditions, provided that at least one of D^a, D^b and D^c is a reducible group.

In one embodiment of the reduction process, compounds of formula (I) may be prepared by reduction of a compound of formula (III) in which

a) D^a represents R_1R_2NCO or $R_1^aCONR_2Alk$, D^b represents $-CH_2NH-$ and D^c represents R_3; or

b) D^a represents R_1R_2NAlk, D^b represents $-CONH-$ or $-CH=N-$ and D^c represents R_3;

with a suitable reducing agent such as a complex metal hydride for example aluminium hydride or lithium aluminium hydride in a solvent such as an ether e.g. tetrahydrofuran or dioxan at a temperature of 20°C to reflux. When the group D^b represents an imino group ($-CH=N-$) the reduction may also be carried out with a borohydride such as sodium borohydride in a solvent such as an alkanol e.g. ethanol at for example 20°C. Alternatively the reduction may be carried out with hydrogen and a metal catalyst such as palladium or platinum.

In another embodiment of the reduction process compounds of formula (I) in which Alk is $-CH_2-$ may be prepared from compounds of formula (III) in which D^a represents $-CHO$, D^b represents $-CH_2NH-$ and D^c represents R_3 by reductive alkylation. Thus the compound (III; D^a is CHO) is reacted with ammonia or an amine R_1R_2NH preferably in a solvent such as tetrahydrofuran or an alkanol, e.g. ethanol, followed by reduction. Suitable reducing agents include hydrides such as sodium borohydride or hydrogen and a metal catalyst such as palladium, platinum or Raney nickel, at for example 20°C.

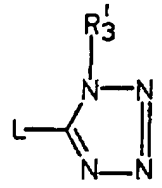
In a further embodiment of the reduction process, a compound of formula (I) in which R_3 represents a hydroxyalkyl group may be prepared from a compound of formula (III) in which D^c is a group that may be reduced to a hydroxyalkyl group e.g. an ester, aldehyde or carboxy group, D^a represents R_1R_2NAlk and D^b represents $-CH_2NH-$. Thus for example a compound of formula (III) in which D^c is $(CH_2)_{q-1}CO_2R_5$ where q is an integer from 2 to 6 and R_5 is hydrogen, alkyl or aralkyl, may be reduced using for example lithium aluminium hydride under the conditions described above to give a compound of formula (I) in which R_3 is the group $(CH_2)_{q-1}CH_2OH$. Compounds of formula (III) in which D^c has the meaning $(CH_2)_{q-1}CHO$ where q is as defined above, may be reduced using sodium borohydride or lithium aluminium hydride or alternatively using hydrogen and a metal catalyst such as palladium or platinum to give a compound of formula (I) in which R_3 is the group $(CH_2)_{q-1}CH_2OH$.

In certain instances it is convenient to reduce for example more than on of the groups D^a, D^b and D^c simultaneously. Thus for xampl compounds of formula (III) in which D^c represents $(CH_2)_{q-1}CO_2R_5$, D^b represents CONH and D^a represents R_1R_2NAlk may be reduced using for example lithium aluminium hydride to give compounds of formula (I) in which R_3 is the group $(CH_2)_qOH$.

Compounds of formula (III) in which D^a represents R_1R_2NCO or CHO, D^b represents CH_2NH and D^c represents R_3 may be prepared by reacting an amine of formula (IV)

$$D^aQX(CH_2)_nY(CH_2)_mNH_2 \qquad (IV)$$

in which D^a represents the group R_1R_2NCO or a protected aldehyde group e.g. an acetal with an aminotetrazole of formula (IV)



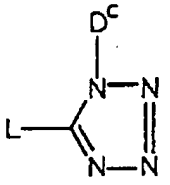
(V)

where L is a leaving group such as halogen e.g. bromine and R_3 is the group R_3 or a group convertible thereto.

Similarly compounds of formula (III) in which D^a represents R_1R_2NAlk, D^b represents CH_2NH and D^c represents $(CH_2)_{q-1}CHO$ (where the aldehyde grouping is preferably protected as e.g. an acetal) or $(CH_2)_{q-1}CO_2R_5$ (where R_5 is hydrogen, alkyl or aralkyl) may be prepared by reacting a diamine of formula (VI)

$$R_1R_2NAlkQX(CH_2)_nY(CH_2)_mNH_2 \qquad (VI)$$

with a tetrazole of the formula (VII)



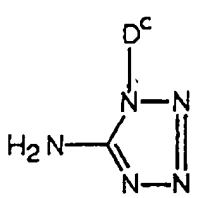
(VII)

where L and D^c are as just defined.

The tetrazoles of formula (VII) are either known compounds or may be prepared by methods analogous to those described in British Patent Specification No. 1364917.

Compounds of formula (III) in which D^a represents $R_1^aCONR_2Alk$ may be prepared by treating the corresponding compounds in which D^a represents HNR_2Alk with an activated derivative of the appropriate acid $R_1^aCO_2H$.

Compounds of formula (III) in which D^b is the group $-CONH-$ may be prepared by reacting the 5-aminotetrazoles (VIII) with an activated derivative of the acid (IX) such as an acid halide, e.g. acid chloride.



(VIII)

$$R_1R_2NAlkQX(CH_2)_nY(CH_2)_{m-1}CO_2H \qquad (IX)$$

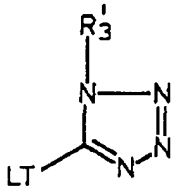
Compounds of formula (III) in which D^b represents $-CH=N-$ may be prepared by condensation of the

5-amino-tetrazoles (VIII) with the aldehyde (X)

$$R_1R_2NAlkQX(CH_2)_nY(CH_2)_{m-1}CHO \qquad (X)$$

The 5-aminotetrazoles (VIII) are either known compounds or may be prepared by methods analogous to those described by R. M. Herbst J. Org. Chem. (1951) *16*, 139 and R. A. Henry, J. Amer. Chem. Soc., (1954), *76*, 93

Compounds of formula (I) may also be prepared by displacement of the group L from a compound of formula (XI)



(XI)

in which R_3' is the group R_3 or a group convertible thereto, L is a leaving group selected from halogen e.g. chlorine or bromine, or a quaternary ammonium group such as trialkylammonium and T represents a bond, $-AlkQX(CH_2)_nY(CH_2)_mNH-$, $-(CH_2)_mNH-$ or $-(CH_2)_nY(CH_2)_mNH-$, by reaction with a nucleophile of formula (XII)

$$R_1R_2NW \qquad (XII)$$

where W respectively represents $-AlkQX(CH_2)_nY(CH_2)_mNH_2$, hydrogen, $-AlkQX(CH_2)_nYH$ or $-AlkQXH$.

Thus in one embodiment of the above process, compounds of formula (I) may be prepared by reaction of a compound of formula (XI) in which L represents halogen preferably bromine and T represents a bond with a compound of formula (XII) in which W represents $-AlkQX(CH_2)_nY(CH_2)_mNH_2$. The reaction is preferably carried out with heating, for example within the range of 100-200°C, in the absence or presence of a solvent such as ethanol, and preferably in a sealed vessel.

In another embodiment of the above process, compounds of formula (I) may be prepared by reacting a compound of formula (XI) in which L represents a trialkylammonium group such as $^{\ominus}AR^aR^bR^cN^{\oplus}$ in which A is an anion e.g. halide and R^a, R^b, R^c are each alkyl or aralkyl e.g. $R^aR^bR^cN^{\oplus}$ is trimethylammonium and T represents $-AlkQX(CH_2)_nY(CH_2)_mNH-$ with a compound of formula (XII) in which W represents hydrogen and in which R_1 and R_2 are other than hydrogen. The reaction is preferably carried out at an elevated temperature, for example 100-150°C.

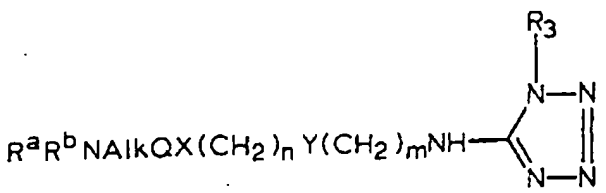
This embodiment is particularly useful for preparing compounds in which Alk is CH_2.

In a further embodiment of this process, compounds of formula (I) in which X is oxygen or sulphur may be prepared from an anion of an alcohol, thiol, phenol or thiophenol, derived from a compound of formula (XII) in which W represents the group $-AlkQX(CH_2)_nYH$ (where Y is oxygen or sulphur) by displacement of the leaving group L from a compound of formula (XI) where L represents halogen preferably chlorine or bromine and T represents $-(CH_2)_mNH-$.

In this reaction the anion derived from the compound of formula (XII) is preferably a phenoxide ion (Q is a benzene ring, X is a bond, n is zero and Y is oxygen). The reaction is carried out by generating the anion, by treating the compound of formula (XII) with a base, e.g. sodium hydride, potassium carbonate or potassium tertiary butoxide in a solvent, e.g. acetone or dimethylformamide at a temperature of 10 to 30°C and then effecting the displacement reaction in the same solvent at temperatures of 25 to 100°C.

Compounds of formula (XI) in which L represents a leaving group such as halogen and T represents a bond are either known compounds or may be prepared by methods analogous to those described in British Patent Specification No. 1,364,917 and G. B. Barlin, J. Chem, Soc., (B), 1967 641.

Compounds of formula (XI) in which L represents a quatermary ammonium group and T represents $-AlkQX(CH_2)_nY(CH_2)_mNH-$ may be prepared by reacting a compound of formula (XIII)



(XIII)

with an alkyl or aralkyl halide e.g. methyliodide or benzyl iodide.

Compounds of formula (XI) in which L represents a leaving group such as halog n and T represents $-(CH_2)_mNH-$ may b prepared by reacting a comp und of formula $HO(CH_2)_mNH_2$ with a compound of formula (XI) in which L is a leaving group such as chlorine or bromine and T r presents a bond, under the conditions described above for the reaction with a diamine (XII) in which W represents $-AlkQX-(CH_2)_nY(CH_2)_mNH_2$, followed by conversion of the hydroxy substituent into a leaving group by standard procedures.

Compounds of formula (I) in which R_3 represents an acyloxyalkyl group may be prepared by reacting a compound of formula (I) in which R_3 represents a hydroxyalkyl group with a carboxylic acid or an activated derivative thereof which corresponds to the acyl group. Suitable activated derivatives include acid halides e.g. acid chlorides and acid anhydrides. When an acid chloride is used, the reaction is preferably carried out in for example pyridine at room temperature.

Where the product of any of the above processes is a free base and a salt is required, the salt may be formed in a conventional manner. Thus for example, a generally convenient method of forming the salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent(s) e.g. an alcohol such as ethanol or an ester such as ethyl acetate.

The invention is illustrated but not limited by the following Examples.

In the following Examples and Preparations temperatures are in °C.

Thin layer chromatography (tlc) and column chromatography were carried out on silica using, unless otherwise stated, one of the following solvent systems.

System A. Dichloromethane : ethanol : 880 ammonia (150:8:1)

System B. Dichloromethane : ethanol : 880 ammonia (100:8:1)

PREPARATION 1

3-[3-[(Dimethylamino)methyl]phenoxy]propionyl chloride

i) *3-[3-[(Dimethylamino)methyl]phenoxy]propionitrile*

A solution of 3-[(dimethylamino)methyl]phenol (201 g), acrylonitrile (477 g) and benzyltrimethylammonium hydroxide (40% methanolic solution, 30 ml) was heated under reflux for 24h. The mixture was evaporated, diluted with ether (500 ml) and filtered. The filtrate was washed with 2N sodium hydroxide and water, dried and evaporated to give the *title compound* (148 g) as a pale yellow oil.

Nmr ($CDCl_3$) : τ2.72, dd, (1H); 2.9 - 3.3, m (3H); 5.83, t, (2H); 6.62, t, (2H); 7.24, t, (2H); 7.79, s, (6H).

ii) *3-[3-[(Dimethylamino)methyl]phenoxy]propionic acid*

A solution of 3-[3-[(dimethylamino)methyl]phenoxy] propionitrile (147 g) in 2N sulphuric acid (800 ml) was heated under reflux for 96h. The pH of the cooled solution was adjusted to pH 7 with sodium bicarbonate and ethanol (2000ml) was added. The mixture was filtered and the filtrate was evaporated and water was removed from the residue by azeotropic distillation with benzene. The resulting oil was triturated with diethylether to give the *title compound* (110 g) as a white powder, m.p. 86 - 89°.

(iii) *3-[3-[(Dimethylamino)methyl]phenoxy]propionyl chloride*

3-[3-[(Dimethylamino)methyl]phenoxy]propionic acid (5.0 g), dichloromethane (120 ml), dimethylformamide (0.5 ml) and thionyl chloride (12 ml) was stirred at room temperature for 3h. The solvent was evaporated off and water was removed from the residual oil by azeotropic distillation with benzene to give the *title compound* as a pale yellow foam (5.5 g).

Ir (nujol mull): 1795 cm^{-1}

PREPARATION 2

a) *N-[1-Methyl-1H-tetrazol-5-yl]-3-[3-(1-piperidinylmethyl)phenoxy]propanamide*

A solution of 3-[3-(1-piperidinylmethyl)phenoxy] propionyl chloride (3.75 g) in dimethylformamide (20 ml) was added to 1-methyl-1*H*-tetrazol-5-amine (1.32 g) in dimethylformamide (30 ml). The mixture was stirred at room temperature for 20h, the solvent was evaporated off to give an oil which was treated with sodium carbonate solution (50 ml) and extracted with ethyl acetate. The extract was washed, dried and evaporated to give the crude product as a gum which was chromatographed using system B to give the *title compound* (1.6 g) as a pale brown foam.

Nmr ($CDCl_3$):τ 1.65, br.s, (1H); 2.83, t, (1H); 3.0 - 3.3, m, (3H); 5.73, t, (2H); 6.03, s, (3H); 6.53, s, (2H); 7.02, t (2H); 7.6, m, (4H); 8.5, m, (6H).

b) Similarly prepared from 4-[3-(1-piperidinylmethyl)phen xy]butyryl chloride (10.7 g) and 1-methyl-1*H*-tetrazol-5-amine (3.6 g), except that the crude pr duct was triturated with cyclohexane and then recrystallised from ethyl acetate, was N-[1-methyl-1*H*-tetraz l-5-yl]-4-[3-(1-piperidinylmethyl)phenoxy]butanamide (3 g) as a pale brown p wder, m.p. 162 - 164°.

c) Similarly prepared from 4-[3-(1-piperidinylmethyl)phenoxy]butyryl chloride (1.5 g) and 1-(1-methylethyl)-1*H*-t traz l-5-amine (0.64 g), except that the crude product was recrystallised from m thanol, was N-[1-[1-(1-methylethyl)]-1*H*-tetrazol-5-yl]-4-[3-(1-piperidinylmethyl)ph noxy] butanamide (0.5 g) as white microcrystals, m.p. 132 - 133°.

d) Similarly prepared from 3-[3-(dimethylaminomethyl)phenoxy]propionyl chloride (5.4 g) and 1-methyl-1*H*-tetrazol-5-amine (2.21 g) was N-[1-methyl-1*H*-tetrazol-5-yl]-3-[3-[(dimethylamino)methyl]phenoxy]propanamide (2.6 g) as a pale yellow foam.
Nmr ($CDCl_3$): τ 0.2, br.s, (1H); 2.8, t, (1H); 3.0 - 3.3, m., (3H); 5.7, t, (2H); 6.05, s, (3H); 6.55, s, (2H); 7.02, t, (2H); 7.73, s, (6H).

e) Similarly prepared from 3-[3-(1-piperidinylmethyl)phenoxy]pripionyl chloride (5.9 g) and 1-phenylmethyl-1*H*-tetrazol-5-amine (3.7 g) was N-[1-phenylmethyl-1*H*-tetrazol-5-yl]-3-[3-(1-piperidinylmethyl)phenoxy]propanamide (2.7 g) as a white powder, m.p. 86 - 89°C.

PREPARATION 3

3-[3-[(1-Methyl-1H-tetrazol-5-yl)amino]propoxy]benzaldehyde

5-Bromo-1-methyl-1*H*-tetrazole (10 g), 3-[3-(1,3-dioxolan-2-yl)phenoxy]propanamine (15 g) and absolute ethanol (20 ml) were heated in an autoclave at 110° for 8h. The solvent was evaporated off, the residue treated with excess sodium carbamate solution and extracted with ethyl acetate. The extract (150 ml) was stirred with 2N hydrochloric acid (250 ml) for 1h and the organic layer was dried and evaporated to give a brown solid which was recrystallised from ethyl acetate to give the *title compound* (4.6 g) as a light brown solid, m.p. 91-92°.

PREPARATION 4

N-[1-ethyl-1H-tetrazol-5-yl]-3-[3-(1-piperidinylmethyl)phenoxy]propanamide

The title compound (2g) was prepared as a light brown oil from 3-[3-(1-piperidinylmethyl)phenoxy]propionyl chloride (5.9g) and 1-ethyl-1*H*-tetrazol-5-amine (1.7g) using the method of preparation 2.
NMR ($CDCl_3$): 2.00, s, (1H); 2.78, dd, (1H); 3.0 - 3.35, m, (3H); 5.5 - 5.8, m, (4H); 6.50, s, (2H); 7.03, t, (2H); 7.56, m, (4H); 8.25 - 8.7, m, (9H).

EXAMPLE 1

1-Methyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-tetrazol-5-amine

A solution of N-[1-methyl-1*H*-tetrazol-5-yl]3-[3-(1-piperidinylmethyl)phenoxy]propanamide (1.4 g) in tetrahydrofuran (100 ml) was added to lithium aluminium hydride (1.4 g) under nitrogen. The mixture was stirred at room temperature for 20h when water (1.4 ml) was added followed by 15% sodium hydroxide solution (1.4 ml) and more water (4.2 ml). The mixture was filtered and the filtrate was evaporated to give a solid which was recrystallised from methyl acetate-hexane to give the *title compound* (1.0 g) as a white solid, m.p. 118 - 119°.

Analysis Found:	C, 61.5;	H, 7.8;	N, 25.1
$C_{17}H_{26}N_6O$ requires:	C, 61.8;	H, 7.9;	N, 25.4%

b) Similarly prepared from N-[1-methyl-1*H*-tetrazol-5-yl]-4-[3-(1-piperidinylmethyl)phenoxy]butanamide (3.1 g), except that dioxan was used as the reaction solvent and the crude product was recrystallised from ether, was 1-methyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-1*H*-tetrazol-5-amine (1.8 g) as a white powder, m.p. 83 - 84°.

Analysis Found	C, 62.7;	H, 8.1;	N, 24.1;
$C_{18}H_{28}N_6O$ requires:	C, 62.8;	H, 8.1;	N, 24.4%

c) Similarly prepared from N-[1-[1-(1-methylethyl)]-1*H*-tetrazol-5-yl]-4-[3-(1-piperidinylmethyl)phenoxy]butanamide (0.4 g), except that the crude product was chromatographed using system A was 1-(1-methylethyl)-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-1*H*-tetrazol-5-amine (54 mg) as a pale brown oil.
Nmr ($CDCl_3$: τ 2.76, dd, (1H); 3.0 - 3.3, m, (3H); 4.82, t, (1H); 5.62, m, (1H); 6.0, t, (2H); 6.45, m, (2H); 6.52, s, (2H); 7.58, m, (4H); 8.10, m, (4H); 8.25 - 8.70, m+d, (12H).
Tlc system A, R_f 0.5

d) Similarly prepared from N-[1-methyl-1*H*-tetrazol-5-yl]-3-[3-[(dimethylamin)methyl]phenoxy]propanamide (2.5g) was 1-methyl-N-[[3-[3-(dimethylamino)methyl]phen xy]propyl]-1*H*-tetrazol-5-amine (1.2g) as white crystals, m.p. 72°.

Analysis F und:	C, 57.9;	H, 7.6;	N, 28.9;
$C_{14}H_{22}N_6O$ requires:	C, 57.8;	H, 7.7;	N, 29.1%

e) Similarly prepared from N-[1-phenylmethyl-1*H*-tetrazol-5-yl]-3-[3-(1-piperidinylm thyl)phenoxy]-

propanamide (2.5g) was 1-phenylmethyl-N-[3-[3-(1-piperidinylmethyl)phen xy]propyl]-1*H*-tetrazol-5-amin hemihydrate (1.2g) as white crystals, m.p. 88 - 90°.

Analysis Found:	C, 66.7;	H, 7.5;	N, 20.5;
$C_{23}H_{30}N_6O.\ ½H_2O$ requires:	C, 66.5;	H, 7.4;	N, 20.2%

EXAMPLE 2

a) *1-Methyl-N-[3-[3-(pyrrolidinylmethyl)phenoxy]propyl]-1H-tetrazol-5-amine hydrate (4 : 1)*

5-Bromo-1-methyl-1*H*-tetrazole (1.0g) (Compound A), 3-[3-[(1-pyrrolidinyl)methyl]phenoxy]propanamine (3.58g) and absolute ethanol (4 ml) were heated at 110° in an autoclave for 48h. The solvent was evaporated, the residue was basified with excess sodium carbonate and extracted with ethyl acetate. The extract was dried and evaporated to give a yellow solid which was recrystallised from methyl acetate : petroleum ether (b.p. 60 - 80°) (1 : 3) to give the *title compound* (0.5g) as white crystals, m.p. 87° (softens).

Analysis Found:	C, 60.1;	H, 7.3;	N, 26.1;
$C_{16}H_{24}N_6O.¼H_2O$ requires:	C, 59.9;	H, 7.7;	N, 26.2%

b) Similarly prepared from compound A (1g) and 2-[[5-(dimethylamino)methyl]-2-furanylmethyl]thio]ethylamine (3.28g), except that the reaction was carried out at 120° for 26h and the crude product was chromatographed using system B to give an oil which was triturated with petroleum ether : methyl acetate (3 : 1), was 1-methyl-N-[2-[[5-(dimethylamino) methyl-2-furanylmethyl]thio]ethyl]-1*H*-tetrazol-5-amine (0.4g) as a white powder, m.p. 68 - 69°

Nmr ($CDCl_3$): 3.9, s, (2H); 4.87, br.s, (1H); 6.23, s, (3H); 6.3, s, (2H); 6.52, q, (2H); 6.62, s, (2H); 7.17, t, (2H); 7.75, s, (6H).

c) Similarly prepared from compound A (0.8g) and 3-[4-(1-piperidinyl)methyl]phenoxy]propanamine (0.86g), except that the reaction was carried out at 125° for 24h, was 1-methyl-N-[3-[4-(1-piperidinylmethyl)phenoxy]propyl]-1*H*-tetrazol -5-amine (0.61g) as a white solid, m.p. 138 - 139°.

Analysis Found;	C, 61.6;	H, 7.9;	N, 25.2;
$C_{17}H_{26}N_{60}$ requires:	C, 61.8;	H, 7.9;	N, 25.4%

EXAMPLE 3

1-Methyl-N-[3-[3-(2,3,4,5,6,7-hexahydro-1-acinyl]phenoxy]propyl]-1H-tetrazol-5-amine

i) *3-[3-[(1-methyl-1H-tetrazol-5-yl)amino]propoxy]-N,N,N-trimethylbenzenemethanaminium iodide*

Methyl iodide (0.33g) in acetonitrile (1 ml) was added to a solution of 1-methyl-N-[3-[3-(dimethylamino) methyl]phenoxy]propyl-1*H*-tetrazol-5-amine (0.62g) in acetonitrile (1 ml) and the mixture stirred at room temperature for 2 h. The precipitate was filtered off, washed with acetonitrile and dried to give the *title compound* (0.38g) as a white solid.

Nmr (D_2O):2.5, t, (1H); 2.85, m, (3H); 5.53, s, (2H); 5.8, t, (2H); 6.24, s, (3H); 6.47, t, (2H); 6.85, s, (9H); 7.85, m, (2H)

ii) *1-methyl-N-[3-[3-(2,3,4,5,6,7-hexahydro-1-acinyl]phenoxy]propyl]-1H-tetrazol-5-amine*

2,3,4,5,6,7-hexahydroazocine (1.41g) and 3-[3-[(1-methyl-1*H*-tetrazol-5-yl)amino]propoxy]-N,N,N-trimethyl-benzenemethanaminium iodide (0.77g) was heated at 125° for 8h. The reaction mixture was dissolved in water and extracted with ethyl acetate. The extract was washed, dried and evaporated to give a solid (1.5g) which was chromatographed using system B to give a white solid (0.25g) which was recrystallised from methyl acetate : petroleum ether (b.p. 60 - 80°) to give the *title compound* (0.10g) as a white powder, m.p. 108°.

Analysis Found:	C, 63.9;	H, 8.4;	N, 23.5;
$C_{19}H_{30}N_6O$ requires:	C, 63.6,	H, 8.4;	N, 23.4%

EXAMPLE 4

5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-tetrazol-1-(2-ethanol) hydrate (4 : 1)

i) *5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-tetrazole-1-acetic acid monopotassium salt hemihydrate*

5-Bromo-1*H*-tetrazole-1-acetic acid (1g), 3-[3-(1-pip ridinylmethyl)phenoxy]propanamine (3g) and ethanol (10 ml) were heated in an autoclav at 100° for 48h. Th mixture was co led, evaporated, basified with s dium carbonate solution and washed with ethyl acetate. The aqueous phase was saturated with p tassium carb nate and extracted with propan-2-ol and the extract with dried (K_2CO_3), heated t reflux and

filtered hot. The filtrate was cooled, centrifuged and filtered to give a solid which was recrystallised from absolute ethanol to give the *title compound* (180 mg) as a white powder, m.p. 211 - 13°

Analysis Found:	C, 51.3;	H, 6.1;	N, 19.6;	K, 9.5;
$C_{18}H_{25}KN_6O_3.½H_2O$ requires:	C, 51.3;	H, 6.2;	N, 19.9;	K, 9.3%

ii) *Ethyl 5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-tetrazol-1-acetate hydrate (4 : 1)*

5-[[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]amino]-1*H*-tetrazole-1-acetic monopotassium salt hemihydrate (1.1g) and concentrated sulphuric acid (0.2g) were refluxed in absolute ethanol (60 ml) for 70h. The mixture was cooled and evaporated, water (50 ml) was added and the solution basified with excess potassium carbonate. The solution was extracted with ethyl acetate and the extract dried and evaporated to give a gum which was crystallised from methyl acetate - petroleum ether (b.p. 60 - 80°) to give the *title compound* (260 mg) as a white powder, m.p. 92 - 95°.

Analysis Found:	C, 59.2;	H, 7.5;	N, 20.4;
$C_{20}H_{30}N_6O_2.¼H_2O$ requires:	C, 59.0;	H, 7.55;	N, 20.6%

iii) *5-[[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]amino]-1H-tetrazole-1-(2-ethanol)hydrate (4 : 1)*

Ethyl 5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1*H*-tetrazole-1-acetate hydrate (4 : 1) (200 mg) and lithium aluminium hydride (200 mg) were stirred at room temperature in THF (10 ml) under nitrogen for 1h. Water (0.2 ml), then 15% sodium hydroxide solution (0.2 ml) and more water (0.6 ml) were then added and the mixture was filtered. The filtrate was evaporated to give a gum which was chromatographed using system B to give a gum which was triturated with ether to give the *title compound* (70 mg) as a white powder, m.p. 86 - 87°.

Analysis Found:	C, 59.3;	H, 7.8;	N, 23.3;
$C_{18}H_{28}N_6O_2.¼H_2O$ requires:	C, 59.3;	H, 7.9;	N, 23.0%

EXAMPLE 5

The following compounds were prepared according to the method of Example 2:

a) From 5-bromo-1-methyl-1*H*-tetrazole (compound A) (0.8g) and 2-[[5-(dimethylamino)methyl-4-methyl-2-furanylmethyl]-thio]ethanamine (1.14 g), using the method of Example 2 except that the reaction was carried out at 125° for 20 h and the crude product was chromatographed using system B to give an oil which was triturated with petroleum ether: ether (3:1), N-[2-[[5-(dimethylamino)methyl-4-methyl-2-furanylmethyl]thio]ethyl]-1-methyl-1*H*-tetrazol-5-amine (0.28 g) was prepared as a light brown solid, m.p. 172 - 3°.

NMR ($CDCl_3$): 3.98, s, (1H); 4.63, t, (1H); 6.20, s, (3H); 6.32, s, (2H); 6.50, q, (2H); 6.64, s, (2H); 7.15, t, (2H); 7.75, s, (6H); 8.02, s, (3H).

b) From compound A (0.8 g) and 2-[[5-(dimethylamino)methyl-2-thienylmethyl]thio]ethanamine (1.14 g) using the method of Example 2 exept that the reaction was carried out at 125° for 18h and the crude product was chromatographed using system B to give an oil which was triturated with ether: petroleum ether (b.p. 60 - 80°) (1:1), N-[2-[[5-(dimethylamino)methyl-3-thienylmethyl]thio]-1-methyl-1*H*-tetrazol-5-amine (0.37 g) was prepared as a white solid, m.p. 54 - 56°.

NMR ($CDCl_3$): 2.97, s, (1H); 3.12, s, (1H); 5.07, t, (1H); 6.23, s, (3H); 6.32, s, (2H); 6.35, q, (2H); 6.44, s, (2H); 7.22, t, (2H); 7.73, s, (6H).

c) From compound A (0.8 g) and 2-[2-[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethylamine (1.39 g), using the method of Example 2 except that the reaction was carried out at 125° for 24h and the crude product was chromatographed using system B to give an oil which was dissolved in ether and treated with excess ethereal hydrogen chloride, 1-methyl-N-[2-[2-[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]-1*H*-tetrazol-5-amine dihydrochloride (0.65 g) was prepared, m.p. 45° (softens).

Analysis Found:	C, 49.6;	H, 6.9;	N, 19.5;
$C_{18}H_{28}N_6O_2$ requires:	C, 499;	H, 7.0;	N, 19.4%

EXAMPLE 6

1-Ethyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-tetrazol-5-amine hydrate (4:1)

The *title compound* (0.69 g) was prepared from N-[1-ethyl-1*H*-tetrazol-5-yl]-3-[3-(1-piperidinylmethyl]phenoxy]propanamide (1.36g) using the method of Example 1 as white microcrystals, m.p. 94-95°.

Analysis Found:	C, 62.2;	H, 8.2;	N, 24.0;
$C_{18}H_{28}N_6O.¼H_2O$ requires:	C, 61.9;	H, 8.2;	N, 24.1%

EXAMPLE 7

(a) *N-[3-[3-[[(2-Furanylmethyl)amino]methyl]phenoxy]propyl]-1-methyl-1H-tetrazol-5-amine hydrate (4:1)*

3-[3-[(1-Methyl-1*H*-tetrazol-5-yl)amino]propoxy]benzaldehyde (1.5g) and furfurylamine (7.5 ml) in ethanol (50 ml) were stirred at 21° for 1.5h. Sodium borohydride (2.0g) was then added and the reaction stirred for a further 18h at 21°. Water (100 ml) was added and the mixture evaporated to 25 ml and extracted with ethyl acetate. The extract was dried and evaporated to give an orange oil (2g) which was chromatographed using ethyl acetate:methanol (9:1) to give a yellow solid (0.92g) which was recrystallised from diethyl ether to give the *title compound* (0.45g) as a white powder, m.p. 55 - 56°.

Analysis Found:	C, 58.8;	H, 6.6;	N, 24.5;
$C_{17}H_{22}N_6O_2.¼H_2O$ requires:	C, 58.8;	H, 6.5;	N, 24.2%

The following compounds were similarly prepared from 3-[3-[(1-methyl-1*H*-tetrazol-5-yl)amino]propoxy]benzaldehyde (Compound B) and the corresponding amine.

b) Compound B (1.25g) and hexylamine (6 ml) gave N-[3-[3-[(hexylamino)methyl]phenoxy]propyl]-1-methyl-1*H*-tetrazol-5-amine hydrate (4:1) (0.54g) as an off-white solid, m.p. 96 - 98°.

Analysis Found:	C, 61.2;	H, 8.4;	N, 23.5;
$C_{18}H_{30}N_6O.¼H_2O$ requires:	C, 61.6;	H, 8.75;	N, 23.9%

c) Compound B (0.62g) and 4-hydroxypiperidine (2.5g) gave 1-[[3-[3-[(1-methyl-1*H*-tetrazol-5-yl)amino]propoxy]phenyl]methyl]-4-piperidinol hemihydrate (0.37g) as a white solid, m.p. 72° (softens)

Analysis Found:	C, 57.6;	H, 7.5;	N, 23.3;
$C_{17}H_{26}N_6O_2.½H_2O$ requires:	C, 57.4;	H, 7.3;	N, 23.6%

d) Compound B (0.67g) and 1,2,5,6-tetrahydropyridine (3 ml) gave 1-methyl-N-[3-[3-[(1,2,5,6-tetrahydropyridinyl)methyl]phenoxy]propyl]-1*H*-tetrazol-5-amine (0.45g) as a white solid, m.p. 77° (softens).

Analysis Found:	C, 62.2;	H, 7.5;	N, 25.5;
$C_{17}H_{24}N_6O$ requires:	C, 62.2;	H, 7.4;	N, 25.6%

EXAMPLE 8

1-Methyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-tetrazol-5-amine citrate (1:1) hemihydrate

A solution of citric acid (94 mg) in ethyl acetate (50 ml) was added to a stirred solution of 1-methyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1*H*-tetrazol-5-amine (143 mg) in ethyl acetate (10 ml) to give a precipitate which was filtered off and washed with ethyl acetate to give the *title compound* ((202 mg) as a white powder was m.p. 35°.

Nmr (D_2O) 2.58, t, (1H); 2.8 - 3.0, m, (3H); 5.8, s, (2H); 5.83, t, (2H); 6.3, s, (3H); 6.45, t, (2H); 6.6, m, (2H); 7.15, m, (2H); 7.2 AB q, (2H); 7.9, m, (2H); 8.0 - 8.7, m, (6H).

Examples of Pharmaceutical Compositions

Tablets	mg/tablet	mg/tablet
Active ingredient	20.0	40.0
Microcrystalline cellulose BPC	99.5	199.0
Magnesium stearate B.P.	0.5	1.0
Compression weight	120.0	240.0

The drug is sieved through a 250 µm sieve, blended with the excipients and compressed using 6.5 mm and 8.0 mm diameter punches for the 20 and 40 mg strengths respectively. Tablets of other strengths may be prepared by increasing the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, e.g. methyl cellulose, ethyl cellulose or hydroxypropylmethyl cellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Injection for Intravenous Administration

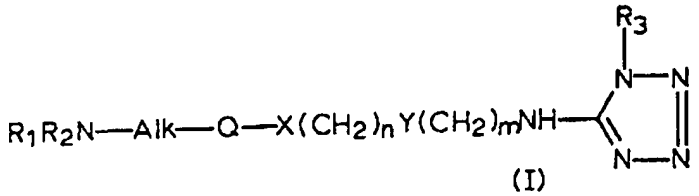
	% w/v
Active ingredient	0.25
Water for Injection BP To	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability using dilute acid or alkali or suitable buffer salts.

The solution is prepared, clarified and filled under nitrogen into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions.

CLAIMS

1. A process for the preparation of compounds of the general formula (I)



(I)

and physiologically acceptable salts, hydrates and bioprecursors thereof in which

R_1 represents C_{1-14} alkyl, cycloalkyl, aralkyl, trifluoroalkyl, heteroaralkyl, alkenyl, alkynyl, or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or a C_{1-4} alkyl group; or

R_1 and R_2 together with the nitrogen atom to which they are attached, form a 5-10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl groups or a hydroxy group and/or may contain another heteroatom selected from oxygen and sulphur;

Alk represents a straight or branched C_{1-6} alkylene chain.

Q represents a furan or thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 5-positions, th furan or thiophen ring optionally bearing a further substituent R_4 adjacent to the group R_1R_2N-Alk-; or Q represents a thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 4-positions, the thiophen ring optionally bearing a further substituent R_4 adjacent to the group R_1R_2NAlk with the proviso that when the group R_1R_2NAlk is in the 4-position then the group R_4 is in the 5-position; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4-positions;

R_4 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, C_{2-6} alkyl substituted by hydroxy, alkoxy or C_{1-4} alkanoyloxy;

X and Y, which may be the same or different, each represent oxygen, sulphur, methylene or a bond;

n represents zero, 1, 2 or 3 and m represents an integer from 2 to 5 with the provisos that (a) the total number of atoms in the chain $X(CH_2)_nY(CH_2)_m$ is an integer from 3 to 8 and (b) when X and Y represent oxygen or sulphur then n is 2 or 3.

2. Compounds as claimed in claim 1 in which the chain $X(CH_2)_nY(CH_2)_m$ contains from 4 to 6 atoms.

3. Compounds as claimed in claim 2 in which the group $X(CH_2)_nY(CH_2)_m$ represents $-O(CH_2)_{3-4}$ and in which Q is a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3-positions.

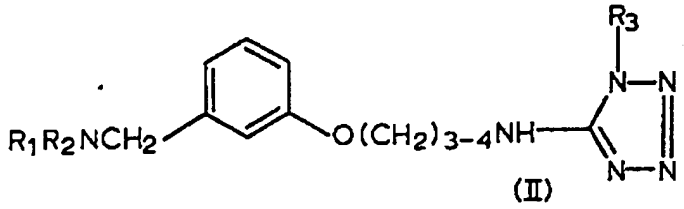
4. Compounds as claimed in any of claims 1 to 3 in which Alk is methylene.

5. Compounds as claimed in any of claims 1 to 4 in which R_3 is C_{1-4} alkyl or hydroxy C_{2-4} alkyl.

6. Compounds as claimed in any of claims 1 to 5 in which R_1 represents C_{1-8} alkyl, or a heteroaryl C_{1-3} alkyl group where the heteroaryl ring contains one hetero-atom; and R_2 represents hydrogen or methyl; or R_1R_2N represents a saturated 5 to 7 membered ring optionally containing a double bond or substituted by a hydroxy group.

7. Compounds as claimed in claim 6 in which R_1R_2N is di C_{1-2} alkylamino or a saturated 5 to 7 membered ring.

8. Compounds as claimed in claim 1, corresponding to the formula (II)



(II)

and physiologically acceptable salts and hydrates thereof, wherein R_1R_2N represents dimethylamino, piperidino or pyrrolidino; and R_3 represents methyl or hydroxyethyl.

9. Compounds as claimed in claim 8 which are:

1-methyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1*H*-tetrazol -5-amine;

1-methyl-N-[[3-[3-(dimethylamino)methyl]phenoxy]-propyl]-1*H*-tetrazol -5-amine;

1-methyl-N-[3-[3-(pyrroldinylmethyl)phenoxy]propyl-1*H*-tetrazol -5-amine; and

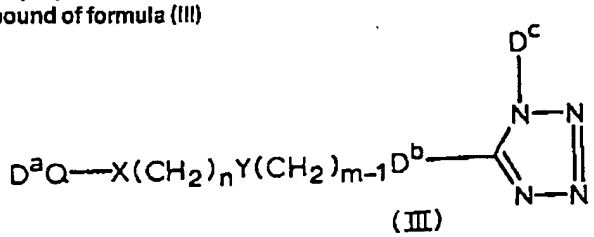
5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1*H*-tetrazol -1-(2-ethanol);

and physiologically acceptable salts and hydrates thereof.

10. Compounds as claimed in claim 1 in which Q is as defined in claim 1 except that it does not represent a thiophene ring incorporated into the molecule through bonds in the 2- and 4-positions and R_3 is as defined in claim 1 except that it does not represent C_{2-6} alkyl substituted by C_{1-4} alkanoyloxy.

11. A process for the preparation of compounds as claimed in claim 1 which comprises

a) reducing a compound of formula (III)



(III)

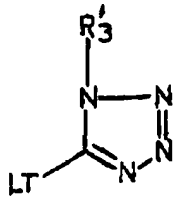
In which

D^a may represent R_1R_2NAlk- or a group convertible th reto under reducing conditi ns;

D^b represents $-CH_2NH-$, $-CONH-$ or $-CH=N$; and

D^c represents R_3 or a group c nv rtible thereto under reducing conditions, provided that at least on f D^a, D^b and D^c is a reducible group; r

b) reacting a compound of formula (XI)



(XI)

in which R_3' is the group R_3 or a group convertible thereto, L is a leaving group selected from halogen and quaternary ammonium groups and T represents a bond, $-AlkQX(CH_2)_nY(CH_2)_mNH-$, $-(CH_2)_mNH-$ or $-(CH_2)_nY(CH_2)_mNH-$, with a nucleophile of formula (XII)

R_1R_2NW (XII)

where W respectively represents $-AlkQX(CH_2)_nY(CH_2)_mNH_2$, hydrogen, $-AlkQX(CH_2)_nYH$ or $-AlkQH$; or

c) for the production of compounds of formula (I) in which R_3 represents an acyloxyalkyl group, reacting a compound of formula (I) in which R_3 represents a hydroxyalkyl group with the carboxylic acid corresponding to the acyl group or an activated derivative thereof;

and where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

12. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 10 and at least one inert pharmaceutically acceptable carrier or diluent, optionally together with at least one other active ingredient.

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